C1

1q21 chromosomal rearrangement which comprises: a) obtaining RNA from the sample from the subject; b) contacting the RNA of step (a) with a nucleic acid molecule of at least 15 contiguous nucleotides capable of specifically hybridizing with a unique sequence included within the sequence of an isolated RNA encoding human IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9), under conditions permitting hybridization of the RNA of step (a) with the nucleic acid molecule capable of specifically hybridizing with a unique sequence included within the sequence of an isolated RNA encoding human IRTA protein, wherein the nucleic acid molecule is labeled with a detectable marker; and c) detecting any hybridization in step (b), wherein detection of hybridization indicates presence of B cell malignancy or a type of B cell malignancy in the sample.

Please delete the paragraph starting on page 8, line 9, and insert the following paragraph:

C2

This invention provides an antibody/antibodies directed to an epitope of a purified IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein, or fragment(s) thereof, having the amino acid sequence set forth in any of Figures 18A (SEQ ID NO:1), 18B-1-18B-3 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), 18C-1-18C-2 (SEQ ID NO:5), 18D-1-18D-2 (SEQ ID NO:7) or 18E-1-18E-2 (SEQ ID NO:9), respectively.

Please delete the paragraph starting on page 8, line 15, and

insert the following paragraph:

C3

This invention provides an antibody directed to a purified IRTA protein selected from the group consisting of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9).

Please delete the paragraph starting on page 8, line 19, and insert the following paragraph:

C4

This invention provides a pharmaceutical composition comprising an amount of the antibody directed to an IRTA protein effective to bind to cancer cells expressing an IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9), so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier.

Please delete the paragraph starting on page 9, line 1, and insert the following paragraph:

C5

This invention provides a method of diagnosing B cell malignancy which comprises a 1q21 chromosomal rearrangement in a sample from a subject which comprises: a) obtaining the sample from the subject; b) contacting the sample of step (a) with an antibody directed to a purified IRTA protein capable of specifically binding with a human IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5),

C5

IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) IRTA protein on a cell surface of a cancer cell under conditions permitting binding of the antibody with human IRTA protein on the cell surface of the cancer cell, wherein the antibody is labeled with a detectable marker; and c) detecting any binding in step (b), wherein detection of binding indicates a diagnosis of B cell malignancy in the sample.

Please delete the paragraph starting on page 29, line 20, and insert the following paragraph:

C6

Nucleic acid molecules encoding proteins designate "MUM-2" (SEQ ID NO:15) and "MUM-3" (SEQ ID NO:17, SEQ ID NO:19 or SEQ ID NO:4)) proteins in the First Series of Experiments are now called "*IRTA-1*" and "*IRTA-2*" genes, i.e. nucleic acid molecules which encode IRTA-1 (SEQ ID NO:1) and IRTA-2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41) proteins respectively. IRTA-3 (SEQ ID NO:5), -4 (SEQ ID NO:7) and -5 (SEQ ID NO:9) proteins are members of the same the immunoglobulin gene superfamily as are the IRTA-1 and IRTA-2 proteins.

Please delete the paragraph starting on page 32, line 4, and insert the following paragraph:

C7

This invention provides a method of producing an IRTA polypeptide (protein) which comprises: (a) introducing a vector comprising an isolated nucleic acid which encodes an immunoglobulin receptor, Immunoglobulin superfamily Receptor Translocation Associated, IRTA, protein into a suitable host cell; and (b) culturing the resulting cell

so as to produce the polypeptide. In further embodiments, the IRTA protein produced by the above-described method may be recovered and in a still further embodiment, may be purified either wholly or partially. In an embodiment the IRTA protein may be any of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) protein. In further embodiments, any of the IRTA proteins may be mammalian proteins. In still further embodiments, the mammalian proteins may be human or mouse IRTA proteins.

Please delete the paragraph starting on page 32, line 20, and insert the following paragraph:

IRTA genes, nucleic acid molecules encoding IRTA proteins IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9), are useful for the production of the IRTA proteins encoded thereby. ITRA proteins are useful for production of antibodies; such antibodies are used as reagents for differential diagnosis of lymphoma subtypes in hematopathology. Antibodies directed against IRTA proteins and which bind specifically to IRTA proteins also have therapeutic uses, i.e. to specifically target tumor cells, which may be used and administered similarly to "Rituximab" (an anti-CD20 antibody), which is an antibody approved by the FDA for therapy of relapsed CD20-positive lymphomas (Foon K., Cancer J. 6(5):273). Anti-IRTA1, anti-IRTA2, anti-IRTA3, anti-IRTA4 and anti-IRTA5 antibodies are also useful markers for isolation of specific subsets of B cells in research

C8

studies of normal and tumor B cell biology. Moreover, anti-IRTA1, anti-IRTA2, anti-IRTA3, anti-IRTA4 and anti-IRTA5 antibodies are useful research reagents to experimentally study the biology of signaling in normal and tumor B cells.

Please delete the paragraph starting on page 33, line 9, and insert the following paragraph:

C9

Methods of introducing nucleic acid molecules into cells are well known to those of skill in the art. Such methods include, for example, the use of viral vectors and calcium phosphate co-precipitation. Accordingly, nucleic acid molecules encoding IRTA proteins IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO;44, 3, 41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) may be introduced into cells for the production of these IRTA proteins.

Please delete the paragraph starting on page 35, line 7, and insert the following paragraph:

C10

This invention provides an isolated nucleic acid molecule comprising at least 15 contiguous nucleotides capable of specifically hybridizing with a unique sequence included within the sequence of the isolated nucleic acid molecule encoding IRTA protein. In an embodiment, the IRTA protein may be IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein, or fragment(s) thereof, having the amino acid sequence set forth in any of Figures 18A (SEQ ID NO:1), 18B-1-18B-3 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), 18C-1-18C-2 (SEQ ID NO:5), 18D-1-18D-2 (SEQ ID NO:7) or

C10

18E-1-18E-2 (SEQ ID NO:9), respectively. In other embodiments, the isolated nucleic acid molecules are labeled with a detectable marker. In still other embodiments of the isolated nucleic acid molecules, the detectable marker is selected from the group consisting of a radioactive isotope, enzyme, dye, biotin, a fluorescent label or a chemiluminescent label.

Please delete the paragraph starting on page 37, line 28, and insert the following paragraph:

C11

In preferred embodiments of the antisense oligonucleotide, the ITRA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) protein. In further embodiments of any of the above-described oligonucleotides of nucleic acid molecules encoding the IRTA1, IRTA2, IRTA3, IRTA4 and/or IRTA5 proteins, the nucleic acid may be genomic DNA or cDNA.

Please delete the paragraph starting on page 38, line 15, and insert the following paragraph:

C12

As used herein, the phrase "specifically hybridizing" means the ability of a nucleic acid molecule to recognize a nucleic acid sequence complementary to its own and to form double-helical segments through hydrogen bonding between complementary base pairs. As used herein, a "unique sequence" is a sequence specific to only the nucleic acid molecules encoding the IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3

(SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) proteins. Nucleic acid probe technology is well known to those skilled in the art who will readily appreciate that such probes may vary greatly in length and may be labeled with a detectable label, such as a radioisotope or fluorescent dye, to facilitate detection of the probe. Detection of nucleic acid molecules encoding the IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) proteins is useful as a diagnostic test for any disease process in which levels of expression of the corresponding IRTA1, IRTA2, IRTA3, IRTA4 and/or IRTA5 proteins is altered. DNA probe molecules are produced by insertion of a DNA molecule which encodes mammalian IRTA1, IRTA2, IRTA3, IRTA4 and/or IRTA5 proteins or fragments thereof into suitable vectors, such as plasmids or bacteriophages, followed by insertion into suitable bacterial host cells and replication and harvesting of the DNA probes, all using methods well known in the art. For example, the DNA may be extracted from a cell lysate using phenol and ethanol, digested with restriction enzymes corresponding to the insertion sites of the DNA into the vector (discussed herein), electrophoresed, and cut out of the resulting gel. The oligonucleotide probes are useful for 'in situ' hybridization or in order to locate tissues which express this IRTA gene family, and for other hybridization assays for the presence of these genes (nucleic acid molecules encoding any of the IRTA1-IRTA5 proteins) or their mRNA in various biological tissues. In addition, synthesized oligonucleotides (produced by a DNA synthesizer) complementary to the sequence of a DNA molecule which

encodes an IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) or IRTA5 (SEQ ID NO:9) protein are useful as probes for these genes, for their associated mRNA, or for the isolation of related genes by homology screening of genomic or cDNA libraries, or by the use of amplification techniques such as the Polymerase Chain Reaction.

C12

Please delete the paragraph starting on page 45, line 4, and insert the following paragraph:

This invention provides an antibody directed to a purified IRTA protein selected from the group consisting of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9). In a preferred embodiment of the anti-IRTA antibody the IRTA protein is human IRTA protein. The IRTA protein may be any mammalian IRTA protein, including a murine IRTA protein. In a further embodiment of any the above-described antibodies, the antibody is a monoclonal antibody. In another embodiment, the monoclonal antibody is a murine monoclonal antibody or a humanized monoclonal antibody. As used herein, "humanized" means an antibody having characteristics of a human antibody, such antibody being non-naturally occurring, but created using hybridoma techniques wherein the antibody is of human origin except for the antigen determinant portion, which is murine. In yet another embodiment, the antibody is a polyclonal antibody.

C13

Please delete the paragraph starting on page 46, line 8, and

insert the following paragraph:

This invention provides a pharmaceutical composition comprising an amount of the antibody directed to an IRTA protein effective to bind to cancer cells expressing an IRTA protein selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9) so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier. The anti-IRTA antibody may be directed to an epitope of an IRTA protein selected from the group consisting of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9). The IRTA proteins may be human or mouse IRTA proteins.

C14

Please delete the paragraph starting on page 48, line 4, and insert the following paragraph:

In an embodiment of the above-described method of diagnosing B cell malignancy, the IRTA protein is selected from the group consisting of IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9). In another embodiment of the method the IRTA protein is human or mouse IRTA protein. In a further embodiment IRTA protein is purified. In a preferred embodiment of this method, the B cell malignancy is selected from the group consisting of B cell lymphoma, multiple myeloma, Burkitt's lymphoma, marginal zone lymphoma, diffuse large cell lymphoma and follicular

C15

C15

lymphoma. In yet another embodiment of this method, the B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT). In another preferred embodiment of this method, the B cell lymphoma is non-Hodgkin's lymphoma.

Please delete the paragraph starting on page 49, line 19, and insert the following paragraph:

This invention provides a method of detecting human IRTA protein in a sample which comprises: a) contacting the sample with any of any of the above-described anti-IRTA antibodies under conditions permitting the formation of a complex between the antibody and the IRTA in the sample; and b) detecting the complex formed in step (a), thereby detecting the presence of human IRTA in the sample. In an embodiment the IRTA protein detected may be an IRTA1, IRTA2, IRTA3, IRTA4 or IRTA5 protein, having an amino acid sequence set forth in any of Figures 18A (SEQ ID NO:1), 18B-1-18B-3 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), 18C-1-18C-2 (SEQ ID NO:5), 18D-1-18D-2 (SEQ ID NO:7) or 18E-1-18E-2 (SEQ ID NO:9). As described hereinabove detection of the complex formed may be achieved by using antibody labeled with a detectable marker and determining presence of labeled complex. Detecting human IRTA protein in a sample from a subject is another method of diagnosing B cell malignancy in a subject. In an embodiment of this method of diagnosis, the B cell malignancy is selected from the group consisting of B cell lymphoma, multiple myeloma, Burkitt's lymphoma, marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma. In yet another

C16

C16

embodiment of this method, the B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT). In another preferred embodiment of this method, the B cell lymphoma is non-Hodgkin's lymphoma.

Please delete the paragraph starting on page 50, line 22, and insert the following paragraph:

This invention provides a method of treating a subject having a B cell cancer which comprises administering to the subject an amount of anti-IRTA antibody effective to bind to cancer cells expressing an IRTA protein so as to prevent growth of the cancer cells and a pharmaceutically acceptable carrier, thereby treating the subject. Growth and proliferation of the cancer cells is thereby inhibited and the cancer cells die. In an embodiment of the above-described method, the IRTA protein is selected from the group consisting of human IRTA1 (SEQ ID NO:1), IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41), IRTA3 (SEQ ID NO:5), IRTA4 (SEQ ID NO:7) and IRTA5 (SEQ ID NO:9). In a preferred embodiment of the above-described method of treating a subject having a B cell cancer, the anti-IRTA antibody is a monoclonal antibody. In another embodiment of the method, the monoclonal antibody is a murine monoclonal antibody or a humanized monoclonal antibody. The antibody may be a chimeric antibody. In a further embodiment, the anti-IRTA antibody is a polyclonal antibody. In an embodiment, the polyclonal antibody may be a murine or human polyclonal antibody. In a preferred embodiment, the B cell cancer is selected from the group consisting of B cell lymphoma, multiple myeloma, Burkitt's lymphoma, mantle cell lymphoma

C17

marginal zone lymphoma, diffuse large cell lymphoma and follicular lymphoma. In another preferred embodiment, the B cell lymphoma is Mucosa-Associated-Lymphoid Tissue B cell lymphoma (MALT). In a further preferred embodiment, the B cell lymphoma is non-Hodgkin's lymphoma. In a preferred embodiment of the above-described method of treating a subject having a B cell cancer, administration of the amount of anti-IRTA antibody effective to bind to cancer cells expressing an IRTA protein is intravenous, intraperitoneal, intrathecal, intralymphatical, intramuscular, intralesional, parenteral, epidural, subcutaneous; by infusion, liposome-mediated delivery, aerosol delivery; topical, oral, nasal, anal, ocular or otic delivery. In another preferred embodiment of the above-described methods, the anti-IRTA antibody may be conjugated to a therapeutic agent. In further preferred embodiments, the therapeutic agent is a radioisotope, toxin, toxoid, or chemotherapeutic agent.

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Please delete the paragraph starting on page 61, line 5, and insert the following paragraph:

Digoxigenin-containing antisense and sense cRNA probes were transcribed with T3 and T7 RNA polymerase, respectively, from linearized pBluescript KS+ plasmids containing coding region of cDNAs, nucleotides 62 to 1681 of IRTA1 (SEQ ID NO:1) and 18 to 2996 of IRTA2 (SEQ ID NO:44, SEQ ID NO:3 or SEQ ID NO:41). Hyperplastic human tonsillar tissue surgically resected from children in Babies' Hospital, Columbia Presbyterian Medical Center was snap frozen in powdered dry ice. Cryostat sections were stored for several days at -80 degrees C prior to

C18

processing. Non-radioactive *in situ* hybridization was performed essentially as described (Frank et al., 1999), except that fixation time in 4% paraformaldehyde was increased to 20 minutes, and proteinase K treatment was omitted. The stringency of hybridization was 68 degrees C, in 5X SSC, 50% formamide. Alkaline phosphatase-conjugated anti-digoxigenin antibody staining was developed with BCIP/NBT substrate.

C18

Please delete the paragraph starting on page 63, line 28, and insert the following paragraph:

Sequence analysis of the breakpoint regions on the derivative chromosomes and alignment with the germline 14q32 and 1q21 loci (SEQ ID NO:24 and SEQ ID NO:26, respectively) revealed that the breakpoint had occurred in the intron between the CH3 and the transmembrane exon of $C\alpha_1$ on chromosome 14. Although the breakpoint region was devoid of recombination signal sequences (RSS) or switch signal sequences (Kuppers et al., 1999), the sequence CTTAAC (underlined on Figure 8B) was present in both germline chromosomes 14 and 1 at the breakpoint junction (SEQ ID NO:25 and SEQ ID NO:27, respectively). One copy of this sequence was present in each of the derivative chromosomes, with a slight modification in the der(1) copy (point mutation in the last nucleotide: C to G). The nucleotides AT preceding CTTAAC on chromosome 1 were also present in both derivative chromosomes (Figure 8B). The translocation did not result in any loss of chromosome 1 sequences. On the other hand, in the chromosome 14 portion of der(1) we observed two deletions upstream of the breakpoint junction: a 16 nucleotide

C19